REMARKS

Applicants thank Examiner Gebreyesus and Examiner Prouty for taking time to conduct the telephonic interview with the undersigned on August 31, 2005.

I. Status of the Claims

Claims 1-21 were originally filed. As the result of a restriction requirement, claims 15-21 have been withdrawn from consideration and later canceled. Claims 3 and 5 have also been canceled. In the final Office Action mailed June 2, 2005, no rejection was raised against claim 4; yet the summary sheet indicated that the claim was objected to. Applicants thus assume that claim 4 is allowable, except for its dependency from a rejected base claim.

According to the present amendment, claims 1 and 14 recite that the RNase A superfamily polypeptide has at least 90% sequence identity to SEQ ID NO:4, which finds support in the specification, *e.g.*, on page 4, lines 4-7. Claims 1 and 14 are also amended to further define X^2 to be a glycine. Claims 2 and 6 are canceled.

This amendment was not submitted in the previous response by Applicants because Applicants in good faith believed that such amendment would not be necessary to overcome the outstanding rejections. Because this amendment adds no new matter and requires no new search, its entry is respectfully requested.

II. Claim Rejections

A. 35 U.S.C. §112, First Paragraph

Claims 1, 2, 6, 7, and 9-14 were rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. Specifically, the Examiner stated that the specification, while enabling for an RNase polypeptide of SEQ ID NO:2 or 4, does not reasonably provide enablement for any RNase polypeptide that is from any source having an N-terminus of SEQ ID NO:9 and is selectively toxic to any source of proliferating endothelial cells.

Applicants respectfully disagree with the Examiner for reasons set forth in the response filed April 8, 2005. To expedite prosecution, however, Applicants have now amended claims 1 and 14 to recite that the claimed RNase polypeptide has at least 90% sequence identity to SEQ ID NO:4, which is EDN amino acid sequence (SEQ ID NO:6) plus five additional amino acids (MGSLHV) at its N-terminus. Because the amino acid sequences of many members of the RNase A superfamily are known in the art, a sequence comparison among these members can provide important suggestions as to how one might modify an exemplary sequence (*e.g.*, SEQ ID NO:4) without loss of function such as cytotoxicity of the molecule. Figure 1 of the application is just such an example of sequence comparison that illustrates not only the existence of highly conserved domains but also the precise location and identity of the conserved amino acid residues. Based on a sequence alignment like the one shown in Figure 1, one of skill in the art would be able to readily modify a member of the RNase A superfamily (*e.g.*, SEQ ID NO:4) within 10% sequence variation and create a functional variant.

As such, Applicants believe that the invention as claimed is properly enabled under 35 U.S.C. §112, first paragraph. The withdrawal of the enablement rejection is therefore respectfully requested.

B. 35 U.S.C. §102/§103

Claims 1, 2, 6, and 8-11 were rejected under 35 U.S.C. §103(a) for alleged obviousness over Sakakibara *et al.* as evidenced by Griffith *et al.* Claims 2 and 6 were also rejected under 35 U.S.C. §103(a) for alleged obviousness over Sakakibara *et al.* in view of Barker *et al.* (1989). Furthermore, claims 12-14 were rejected under 35 U.S.C. §103(a) for alleged obviousness over Sakakibara *et al.* in view of Griffith *et al.* Applicants respectfully traverse these rejections in light of the present amendment.

In order to establish a *prima facie* showing of obviousness, three requirements must be satisfied: all limitations of a pending claim must be expressly or impliedly disclosed by prior art references; there must be a suggestion or motivation in the art for one skilled artisan to

combine the limitations; and there must be a reasonable expectation of success in making such a combination. MPEP §2143.

As amended, the pending claims are directed to an isolated RNase A superfamily polypeptide, which, among other things, has a defined N-terminal sequence of $MGSLX^3V$. In this N-terminal sequence, X^3 can be any amino acid. In contrast, the Sakakibara reference describes an RNase isolated from urine of pregnant women, RNase UpI-2, which apparently has the N-terminal sequence of SLHV. Yet this reference does not provide an RNase that has an N-terminal sequence fitting the profile of $MGSLX^3V$. This missing limitation is not provided by Griffith *et al.*, which provides evidence of UpI-2 cytotoxicity. Nor can this limitation be found in Barker *et al.*, which is cited to show the complete sequence for human EDN and its putative signal peptide cleavage site. Thus, not all limitations of the pending claims are found in the cited references.

Applicants further contend that nothing can be found in the three references that suggests the modification of the N-terminus of an RNase by adding an N-terminal segment of $MGSLX^3V$. Thus, the cited references do not provide suggestions to further modify the N-terminal sequence of an RNase to arrive at $MGSLX^3V$.

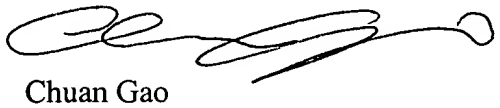
The withdrawal of the rejections under 35 U.S.C. §103(a) is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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